UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/855,486	04/07/97	BAEKKESKOV	S	023070-3122

HM11/0122

TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER 8TH FLOOR
SAN FRANCISCO CA 94111-3834

EXAMINER	
TUNG, M	
ART UNIT	**PAPER NUMBER**
1644	11

DATE MAILED: 01/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/838,486	Applicant(s) Baekkeskov
	Examiner Mary Tung	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Nov 2, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *31, 34, 35, 38-42, and 49-57* is/are pending in the application.

Of the above, claim(s) *38-42* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *31, 34, 35, and 49-57* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Serial No. 08/838,486
Art Unit 1644

DETAILED ACTION

1. Claims 1-30 and 43-48 were cancelled in the preliminary amendment filed April 7, 1997.

2. Claims 32, 33, 36 and 37 have been cancelled in the amendment filed [illegible] 1998 Paper No. 9).

3. Non-elected claims 38-42 were withdrawn from consideration by the Examiner, as per paper mailed April 28, 1998 (Paper No. 6).

4. Claims 49-57 were added in the amendment filed Nov. 2, 1998 Paper No. 9).

5. Claims 31, 34, 35, 38-42 and 49-57 are pending in this application.

In view of the amendment filed November 2, 1998, only the following rejections remain:

***Claim Rejections* - 35 U.S.C. § 112**

6. Applicant's arguments filed November 2, 1998 have been fully considered but they are not persuasive.

7. Claims 31, 34 and 35 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons set forth in the office action mailed April 28, 1998.

8. The applicants argue that "it is sufficient that the claimed methods produce a discernable beneficial effect in at least some patient" and "The burden is on the Examiner to show that it is more likely than not that such minimal level of utility could not be achieved, or could only be achieved with undue experimentation." However, the requirement of utility is an argument under *35 U.S.C. 101*, a rejection not made by the Examiner in the instant case. 35 U.S.C. 112, first paragraph states that the "specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same". Thus, the requirement under 35 U.S.C. 112, first paragraph is not whether a minimal level of utility could be achieved, but rather whether one of skill in the art can make or use the invention as disclosed. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The

factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, the lack of working examples, and the amount of direction or guidance presented.

9. The applicant also argue that "the diagnostic methods of the application allow identification of prediabetic patients, and hence therapeutic invention, before irreversible damage has occurred." The applicants also argue that "general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art at the date of the invention." and therefore "undue experimentation would not be expected to be required to obtain at least some benefit in at least some patients for administration of GAD." Given the disclosure on page 6 and in Fig. 8 of the specification, the Examiner agrees that the onset of IDDM may be predictable using the methods disclosed in the instant application and therefore, prophylaxis of these diseases may be currently possible and therapy may be initiated in these conditions prior to the onset of disease symptoms. However, Tisch, et al. (X) teaches (page 437, col. 1) that the effectiveness of this therapy hinges on several factor: one is whether the therapy can be used to treat an ongoing autoimmune response or whether it is useful only in preventing the disease, and the applicants have failed to disclose a method of treatment using GAD that would actually prevent the onset of IDDM. Additionally, the applicants have failed to disclose whether treatment of an ongoing T-cell-mediated autoimmunity by administering GAD would have an immunizing effect and exacerbate the disease condition. The teaching by Benjamani and Leskowitz ((U2) page 256, paragraph 2) is that "tolerance *can* be induced by opposite extremes of dosage." This teaching by Benjamani and Leskowitz is vague and does not cure the lack of disclosure by the applicants of what range of dosage of GAD would be administered, and what the extremes of dosage would be. The applicants have also failed to disclose how the GAD would be administered, since route of administration is also a key factor in determining whether an immunogenic or tolerogenic response is induced, or whether frequent treatment over a prolonged period of time may result in unforseen immunological complications. Furthermore, in light of the applicants' disclosure on page 20, lines 16-19, that "care should be taken that administration of the pharmaceutical compositions of the present invention does not potentiate the autoimmune response.", there is a lack of guidance in the specification as to how the potentiation of the autoimmune response would be prevented using the instant disclosure.

10. Additionally, the applicants argue that "it would be expected that inducing tolerance to GAD65 would abort subsequent events in the cascade of events leading to IDDM. However, while Tian, et al. (U3) teach that they could induce an antigen-specific anti-inflammatory Th2 response and inhibit disease progression in NOD mice, Tian describes a 65kD GAD antigen, whereas the applicants have disclosed a 64kD GAD antigen, disclosed by the applicants on page 4 as being different with respect to hydrophobicity, solubility and isoelectric point (see lines 20-31). Also, Tian, et al.

teach that treatment of NOD mice and humans at risk for IDDM may differ due to the "complexity of the autoreactive T-cell population and the genetic diversity of MHCs within the [human] patient population." The applicants have not taught how to use their invention to deal with the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM and rheumatoid arthritis, in which there are responses to several antigens ((X), see page 437, col. 2 ¶ 3 and bridging over to col. 3, ¶ 4). It is also unclear whether Tisch, et al. (BO), Kaufman (BG), or Peterson, et al., (W2), teach the same GAD protein as the applicants. Pleau, et al. could not be considered since a copy of the reference was not supplied by the applicants.

11. Additionally, the applicants argue that Lernmark (W) is not applicable as a teaching of enablement since "the issue in determining enablement is not how the method works, but whether the claimed method would result in at least some benefit in al least some patients." This argument based on 35 U.S.C. 101 has been discussed, *supra*. the applicants have not addressed the issue that Lernmark teaches that "Further experiments also extended to the spontaneously diabetic BB rat are warranted to determine the mechanism of protection, especially *as other investigators have not found the published procedures to be easily reproducible.*" ((W), see page 274, col. 2, paragraph 1, in particular). Given the lack of reproducibility tin the art taught by Lernmark, the lack of working examples in the instant application would not allow one of skill in the art to practice the invention as claimed.

12. The applicants also argue that "Harrison recognizes that GAD is a "strong candidate" for therapeutic use (at page 724)." Moreover, "it is 'improper for Office personnel to request evidence of safety in the treatment of humans.'". However, in order for the recited method of treatment to be successful, undue toxicity to the subject must be avoided. The Examiner is not requiring the applicants to provide toxicity data in humans, especially in light of the lack of the limitation of human treatment in any of the claims, but merely to provide a disclosure that one of skill in the art would be able to use to practice the invention as disclosed, in light of the teachings in the art that caution must be exercised in using GAD to treat IDDM. If such a disclosure were made, the lack of toxicity would be inherent in the treatment. Applicant has provided only in vitro experiments demonstrating the identity of GAD in rat islets of Langerhans and in rat brain, and anti-GAD antibodies in the sera of patient with IDDM and stiff man syndrome, to demonstrate operability of the claimed polypeptide. Since applicant has given no guidance as to how their peptide specific therapy would overcome autoreactive T cell escape mechanisms or whether the peptide would induce autoimmunity or tolerance, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

13. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trial and errors to practice the claimed invention. It is suggested that the applicants submit evidence in support of the enablement that administration of GAD protein ameliorates diabetic phenomena (see: Elliott, et al., Diabetes 43:1494(1994) and/or Petersen, et al., Diabetes 44:1478 (1994)).

Claim Rejections - 35 U.S.C. § 102

14. The rejections under 35 U.S.C. 102(a) of claims 31 and 35 as anticipated by Atkinson (WO 90/07117) are hereby withdrawn in light of the argument under paragraphs 22-23 of paper No. 9.

15. Although the '117 patent teaches the administration of 64K proteins or hybrid 64K proteins to prevent or slow the onset of IDDM (see page 7, lines 5-10, and page 33, line 25 and bridging over to page 35, line 20) and a composition containing the 64K antigen, (see the title and page 31, lines 10-16, and claims 15-17, in particular), the '117 patent does not teach a working example wherein such treatment was successful in light of the disclosure by the applicants that mg quantities are needed to treat a single patient and also in light of the exhibit of the declaration from pending case 08/452,053 of Dr. Baekkeskov that only μg quantities can be purified from islet of Langerhans preparations. It is noted, however, that the applicants themselves have not disclosed a working example wherein such treatment was successful, as discussed under 35 U.S.C. 112, first paragraph, *supra*.

16. The rejections under 35 U.S.C. 102(b) of claim 35 as anticipated by a Chang and Gottlieb (AX) are hereby withdrawn in light of the argument under paragraphs 24-25 of paper No. 9.

The following are new grounds for rejection:

17. Claim 31 is rejected under 35 U.S.C. 102(a) as being anticipated by Atkinson (US Patent No. 5,762,937).

18. A method for inhibiting the development of IDDM comprising the administration to a patient GAD is taught in col. 4, lines 40-48 and col. 25 line 53 and bridging over to col. 26, line 14. The administration of a therapeutically-effective dosage is inherent in the successful treatment of any disease. Therefore, the reference teachings anticipate the claimed invention. Any arguments regarding enablement are moot, since the claimed invention of an issued US patent is to be presumed valid.

The following new grounds for rejection are necessitated by the amendment filed November 2, 1998 (Paper No. 9):

Claim Rejections - 35 U.S.C. § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 34 and 49-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, the lack of working examples, and the amount of direction or guidance presented.

21. The goal of peptide immunotherapy of T-cell-mediated autoimmunity is to induce anergy in self reactive T cells. Therefore, the pathologies of autoreactive T cells in autoimmunity can be blocked by using the appropriate autoantigen or autoantigen-derived peptides (see Tisch, et al., (X), page 437, col. 1, in particular). However, the effectiveness of this therapy hinges on several factor: one is whether the therapy can be used to treat an ongoing autoimmune response or whether it is useful only in preventing the disease. Typically, an autoimmune disease is diagnosed at the time of onset when significant tissue damage has already occurred. The onset of IDDM is not predicable and therefore, prophylaxis of these diseases is not currently possible; currently, therapy is initiated in these conditions only after the onset of disease symptoms. Furthermore, Tisch et al., (X) teach that treating an ongoing T-cell-mediated autoimmunity by administering an antigen peptide may have an immunizing effect and exacerbate the disease condition ((X), page 437, column 3, in particular). How the antigen is administered is also a key factor in determining whether an immunogenic or tolerogenic response is induced. The duration of the toleragenic effect is an additional factor. Frequent treatment over a prolonged period of time may result in unforseen immunological complications. Furthermore, the applicant discloses on page 20, lines 16-19, that "care should be taken that administration of the pharmaceutical compositions of the present invention does not potentiate the autoimmune response." There is a lack of guidance in the specification as to how the potentiation of the autoimmune response would be prevented using the instant invention. Additionally, the

high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM and rheumatoid arthritis, in which there are responses to several antigens ((X), see page 437, col. 2 ¶ 3 and bridging over to col. 3, ¶ 4). Additionally, Lernmark (W) teaches that "The mechanisms of GAD65-induced protection of spontaneous diabetes is critical to our understanding of autoimmune diabetes. Further experiments also extended to the spontaneously diabetic BB rat are warranted to determine the mechanism of protection, especially as other investigators have not found the published procedures to be easily reproducible." ((W), see page 274, col. 2, paragraph 1, in particular). Additionally, Harrison (V) teaches that "Insulin and GAD are strong candidate toleragens for the prevention of human IDDM. However, caution should be exercised with GAD because, unlike insulin, it is not β cell specific and is found in high concentrations in the brain as well as in peripheral tissues other than islets. Without further animal studies and knowledge of the GAD epitopes that elicit T cell reactivity unique to human β cells, it would seem unwise to manipulate immunity to this widely distributed key enzyme. For the present, insulin (or proinsulin) is the only islet antigen that, both on scientific and ethical grounds, justifies therapeutic application to humans at risk of IDDM." ((V), see page 724, col. 2, paragraph 2, in particular). Applicant has provided only in vitro experiments demonstrating the identity of GAD in rat islets of Langerhans and in rat brain, and anti-GAD antibodies in the sera of patient with IDDM and stiff man syndrome, to demonstrate operability of the claimed polypeptide. Since human and rats display different major histocompatibility complex haplotypes and applicant has given no guidance as to how their peptide specific therapy would overcome autoreactive T cell escape mechanisms in humans or whether the peptide would induce autoimmunity or tolerance, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

22. The specification fails to provide guidance as to how to determine which amino acid fragments would have the activity recited in claim 34. The specification also fails to provide guidance as to how to modify the intact enzyme that would decrease binding to an associated T-cell receptor while maintaining binding to the major histocompatibility complex, whereby the cellular immune response is inhibited. Detailed information regarding the structural and functional requirements of the GAD protein is lacking. Therefore, predicting which amino acid fragments or modified enzyme would maintain function is well outside the realm of routine experimentation; thus a skilled artisan would require guidance, such as information regarding the location, size, and sequence of deletions and modifications would be required to obtain modified fragments or modified enzyme that would have the recited inhibitory function. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention.

Claim Rejections - 35 U.S.C. § 103

23. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(a) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 35 and 54-57 are rejected under 35 U.S.C. 102(b) as being obvious over Chang and Gottlieb (AX).

26. Chang and Gottlieb (AX) teach the use of GAD in a pharmaceutical preparation by immunizing a mouse with purified rat brain GAD in a composition comprising GAD and Freund's adjuvant (see page 2124, col. 2, paragraph 3, in particular). Chang and Gottlieb do not teach a composition comprising GAD in a pharmaceutically-acceptable carrier for use in humans. However, one of ordinary skill in the art at the time the invention was made would have been motivated to provide a pharmaceutically-acceptable carrier for humans in light of the teaching by Chang and Gottlieb of a pharmaceutically-acceptable carrier for use in rats. Additionally, pharmaceutical carriers are well known to one of ordinary skill in the art for use in humans. Claims 54-56 are included because a product is a product, regardless of its source. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

27. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

Conclusion

28. The Examiner notes and appreciates the applicants' request to review possible pending applications from the patent families of Atkinson and Tobin for interference issues.

29. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

30. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Monday through Friday from 8:30 am to 5:30 pm. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

David A. Saunders
DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644

January 19, 1999
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640